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(54) Stable emulsions of highly fluorinated organic compound.

(57) Stable emulsions of highly fluorinated organic compounds for use as oxygen transport agents, "artificial bloods" or red blood cell substitutes and as contrast agents for biological imaging. The emulsions comprise a highly fluorinated organic compound, an oil that is not substantially surface active and not significantly soluble in water, a surfactant and water.

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STABLE EMULSIONS OF HIGHLY FLUORINATED ORGANIC COMPOUNDS.

5 This invention relates to stable emulsions of
highly fluorinated organic compounds and to processes
of making and using them. Such emulsions are
especially useful in compositions for use as oxygen
transport agents, "artificial bloods" or red blood
10 cell substitutes and as contrast agents for biological
imaging.

Highly fluorinated organic compounds are well
known to be chemically and pharmaceutically inert and
to be capable of dissolving and transporting large
15 amounts of oxygen. These properties make them
potentially useful as oxygen transport agents,
"artificial bloods" or red blood cell substitutes and
as contrast agents for various imaging modalities,
such as nuclear magnetic resonance, ultrasound, and
x-ray. For medical uses that require intravascular
20 injection, highly fluorinated organic compounds must
be dispersed as physiologically acceptable emulsions
as they are too hydrophobic to be miscible with blood.
(See, e.g., L.C. Clark, Jr. et al., "Emulsions of
Perfluorinated Solvents For Intravascular Gas
25 Transport", Fed. Proc., 34(6), pp. 1468-77 (1975); K.
Yokoyama et al., "A Perfluorochemical Emulsion As An
Oxygen Carrier", Artif. Organs (Cleve), 8(1), pp.
34-40 (1984); and United States Patents 4,110,474 and
30 4,187,252).

To date, however, the medical usefulness of
such emulsions as "artificial bloods" or blood
substitutes, oxygen transport agents or contrast
agents for biological imaging has not been as
successful as hoped. This results from the fact that

in practice it has not been previously possible to make emulsions that are both stable and incorporate the relatively large amounts of highly fluorinated organic compounds that are required in clinical
5 practice where the total volume of emulsion that can be administered is limited, e.g., as "artificial bloods". Moreover, it has not been previously possible to make such emulsions using highly
10 fluorinated organic compounds that are excreted from the body within a clinically acceptable time period (see United States Patent 3,911,138). Finally, even those, admittedly less than therapeutically
15 acceptable, compositions that have been available to date are difficult to sterilize because of their instability at high temperature.

Various attempts have been made to prepare stable emulsions containing high concentrations of clinically suitable highly fluorinated organic compounds but none has been successful. To date only
20 one fluorocarbon emulsion has reached clinical testing as an "artificial blood" and that is "Fluosol DA 20%", which is about a 12% by volume emulsion of two fluorocarbons --perfluorodecalin and
25 perfluorotripropylamine -- in a mixture of two surfactants -- yolk phospholipid and Pluronic F-68. The disadvantages of Fluosol DA 20% are firstly that it is not stable in the liquid state and must be
30 stored frozen (Yokoyama et al., supra). Secondly, the required presence of the perfluorotripropylamine in this emulsion, to help "stabilize" it, disadvantages the emulsion's medical usefulness because the half-life of the perfluorotripropylamine in the liver and other body tissues is longer than desirable (see,

e.g., K. Yokoyama et al., supra). Finally, because this emulsion contains only about 12% fluorocarbon by volume, it is much less therapeutically effective than desired because of its low oxygen content capacity (see, e.g., "Fluosol-DA As A Red Cell Substitute In Acute Anemia", N.E. Jour. Med., 314, pp. 1653-66 (1986)).

Therefore, the medical and non-medical uses of highly fluorinated organic compounds as effective oxygen transport agents, "artificial bloods" or red blood cell substitutes, and contrast agents for biological imaging is still a long sought and important goal.

An emulsion in accordance with the invention comprises at least one highly fluorinated organic compound, an oil that is not substantially surface active and not significantly soluble in water, a surfactant and water.

The preferred emulsions of the invention are stable at room temperature for long periods of time. They exhibit substantially no phase separation and substantially no change in particle or droplet size distribution during storage. Moreover, they permit the use of highly fluorinated organic compounds that exhibit acceptably rapid excretion times from the liver and other body tissues, and, they permit the use of the high concentrations of fluorocarbons thereby producing the high oxygen content capacity emulsions required for use of the emulsions of this invention as therapeutically effective blood substitutes. Finally, because of their stability, the emulsions of this invention may be sterilized by heating them to high temperature, for example, 115°C for 15 min. Even such

harsh conditions do not cause phase separation of the emulsions of this invention. As a result of these novel and unexpected properties, the emulsions of this invention solve the long standing problems relating to
5 prior fluorocarbon containing compositions.

This invention also includes methods of making these emulsions and methods and compositions of using them as oxygen transport agents, "artificial bloods" or red blood cell substitutes, and contrast agents for
10 biological imaging.

This invention also includes the use of perfluoroindane or an emulsion thereof as a gas transport agent or NMR contrast agent in animals without causing gas or vapor pulmonary embolism.

15 We believe that the emulsions of this invention may have the highly fluorinated organic compound dispersed in oil and that oil-fluorocarbon combination emulsified in the water and surfactant. However, other possible phases and interfaces are also
20 within the scope of this invention.

Among the highly fluorinated organic compounds that are useful in the emulsions and processes of this invention are those previously said to be useful as oxygen transport agents, "artificial bloods" or red
25 blood cell substitutes, and contrast agents for biological imaging. These include, for example, perfluorocarbons, partially fluorinated hydrocarbons and derivatives and mixtures of them. For example, among the fluoro-containing compounds useful in the
30 emulsions of this invention are 9-18C perfluorohydrocarbons, e.g., perfluorodecalin, perfluoro-trimethyl-bicyclo (3.3.1) nonane and perfluoro-2, 2,4,4-tetramethylpentane, 9-12C perfluoro-

amines, e.g., perfluorotripropylamine, perfluorotributylamine, perfluorodimethyladamantane, perfluoro-1-aza-tricyclic amines, bromo- or iodo-substituted fluorocarbons, and

5 F-4-methyloctahydroquinolidizine. Such compounds are described, for example, in United States Patents 3,962,439; 3,493,581; 4,110,474; 4,186,253; 4,187,252; 4,252,827; 4,423,077; 4,443,480; 4,534,978 and 4,542,147, European Patent Applications 10 80710 and 158,996, British Patent Specification 1,549,038 and German Offen. 2,650,586. Mixtures of any of these highly fluorinated organic compounds may also be used in the emulsions and processes of this invention.

15 Preferably, the emulsions of this invention contain one or more of a perfluorocarbon and most preferably a fluorocarbon selected from the group consisting of perfluorodecalin, perfluorodimethyladamantane, perfluorooctylbromide, perfluoro-4-methyl-20 octahydroquinolidizine, perfluoro-N-methyl-decahydroquinoline, F-methyl-1-oxa-decalin, perfluoro-bicyclo (5.3.0) decane, perfluoro-octahydroquinolidizine, perfluoro-5,6-dihydro-5-decene, perfluoroindane, perfluorotrimethylcyclohexane, perfluoroisopropylcyclohexane and perfluoro-4,5-dihydro-4-octene. For use 25 as a contrast agent for biological imaging perfluorooctylbromide is one of the preferred highly fluorinated organic compounds according to this invention.

30 While the highly fluorinated organic compounds or mixture of such compounds may comprise up to about 75% (by volume) of the emulsions of this invention, preferably, the emulsions of this invention comprise from 10% to about 70% (by volume) f

the fluorocarbon. When the emulsions are to be used as "artificial bloods" or red blood cell substitutes, the fluoro-containing compounds are preferably present in as high a volume concentration as possible. 5 However, 40% (by volume) is often preferred because that concentration matches the approximate oxygen content capacity of whole blood.

Among the not substantially surface active and not significantly water soluble oils that are 10 useful in the emulsions and processes of this invention are liquid fatty oils, hydrocarbons, waxes, such as monoesters of a fatty acid and a monohydroxide alcohol, long chain ethers, diglycerides, silicone oils and nitriles. These include, for example, 15 palmitoyl oleate, octyl nitrile, dodecyl nitrile, soy oil, safflower oil, hexadecane, diglycerides having a C_{12-18} carbon chain and one unsaturation, and mineral oil. As with the fluoro-containing component, these oils also may be used singly or in 20 various combinations in the emulsions and processes of this invention. When our emulsions are to be used medically, the oil or combination of oils must, of course, be physiologically acceptable. For example, when our emulsions are to be used as "artificial 25 bloods", we preferably use physiologically acceptable liquid fatty oils.

The amount of oil, or oils, present in the emulsions of this invention may vary over a wide range of concentrations. It depends on the concen- 30 tration and properties of the other components of the emulsion, being principally dependent on the characteristics of the fluorocarbon component of the emulsion. The actual oil concentration to produce

an acceptable emulsion for any given set of components is easily determined as taught by this invention using simple techniques of preparing and testing the stability of emulsions at various oil concentrations. Within this teaching, we typically employ between about 10 and 30% (by weight of the remaining non-fluorocarbon volume of the emulsion) of oil or a mixture of oils. Preferably, we employ between about 15 and 20% by weight.

Among the surfactants useful in the emulsions of this invention are any of the known anionic, cationic, non-ionic and zwitter-ionic surfactants. These include, for example, anionic surfactants, such as alkyl or aryl sulfates, sulfonates, carboxylates or phosphates, cationic surfactants such as mono-, di-, tri-, and tetraalkyl or aryl ammonium salts, non-ionic surfactants, such as alkyl or aryl compounds, whose hydrophilic part consists of polyoxyethylene chains, sugar molecules, polyalcohol derivatives or other hydrophilic groups and zwitter-ionic surfactants that may be combinations of the above anionic or cationic groups, and whose hydrophobic part consists of any other polymer, such as polyisobutylene or polypropylene oxides. Again, combinations of these surfactants may, of course, be used in the emulsions of this invention. In addition, mixtures of compounds, one or more of which are not surfactants, but which compounds when combined act as surfactants may also be usefully employed as the surfactant component of the emulsions of this invention.

Again, when the emulsions of this inven-

tion are to be used in "artificial bloods" or red blood cell substitutes, the surfactant, or combinations of them, must be physiologically acceptable. For example, in "artificial bloods" we prefer non-
5 ionic surfactants. Preferably, the surfactants used in the emulsions of this invention are one or more of the following: egg phosphatides, lecithin, and alkyl salts of oleic acid, such as sodium oleate.

While the amount of a particular surfactant
10 used in the emulsions of this invention depends on the amounts and properties of the other components of the emulsion, typically we employ about 0.5 to .7% (by weight of the non-fluorocarbon volume) of surfactant. More preferably, we use about 1-2% (by
15 weight).

In addition to the highly fluorinated organic compounds, oils, surfactants and water, the emulsions of this invention may also contain other components conventionally used in "artificial bloods"
20 or blood substitutes, oxygen transport agents or contrast agents for biological imaging. For example, when used as a blood substitute, an emulsion according to this invention should contain an isotonic agent, typically glycerol, to adjust the osmotic
25 pressure of the emulsion to about that of blood. Typically we use about 2.5% (by weight of the non-fluorocarbon volume) of glycerol. However, other amounts and other osmotic pressure controlling agents, e.g., Tyrode solution, could as well be used. The
30 emulsions of this invention may also include other components, such as oncotic agents, e.g., dextran or HES, and antioxidants.

The emulsions of this invention may be

prepared using any order of mixing the four main components of our emulsions - highly fluorinated organic compound, oil, surfactant and water. However, for an optimal emulsion we prefer to mix the fluorocarbon first with the oil in the presence of a combination of all or part of the surfactant and some water. We then prepare the final emulsion by emulsifying this first emulsion in the remaining water and any remaining surfactant.

The mixing and emulsification of our components may be done using any of the conventional mixers and emulsifiers. For example, we may employ Fisher brand touch mixers and Microfluidizers. We may also, if desired, reduce the size of the average droplets or particles in our emulsions by conventional grinding.

In one form of the invention, for example, perfluoroindane is emulsified in water with suitable surfactant. In another form, perfluoroindane is emulsified in a previously prepared intravenous emulsion. Emulsions containing from about 20 to about 50% or more of the perfluoroindane by volume in water may be prepared.

Emulsifying agents are included in the order of about 1 to 10%, exemplified by egg phosphatide, phospholipid or polyoxyethylene-polyoxypropylene copolymer having molecular weight of about 8200 (Pluronic F-68). Other types of surface active agents may be used, including, albumin, glycerol, dextrans, gelatin or other naturally occurring surfactants. The non-ionic surfactants, which do not cause haemolysis are preferred. In addition to the perfluoroindane and surface

active agent in the emulsion, it is preferred, but not essential, that the emulsion include an ionic component. Because most of the surfactants have sizeable osmotic activity, some consideration has to be given to modifying the ionic composition so as not to have a hypertonic solution. Generally speaking, in preparation of emulsions, there is added approximately 0.6 to 0.9% by weight sodium chloride since this is a concentration which can be infused rather rapidly without causing hemolysis. Ringer solution as is or diluted to half-strength with water is suitably used. Oxygen transport is facilitated in the coronary artery by introduction of perfluoroindane or liquid compositions containing perfluoroindane. An isolated organ of an animal may be perfused with perfluoroindane or liquid composition containing same. Furthermore, the perfluoroindane compositions of this invention may be employed utilizing NMR techniques according to procedures reported in U.S. Patent No. 4,586,511.

The following non-limiting examples illustrate various embodiments of this invention.

Example 1

In this example, we prepared two emulsions in the same manner to compare their stabilities. The first emulsion was a conventional composition comprising 40% by volume perfluorodecalin and 60% by volume of a mixture of water (96.3% by weight), lecithin (1.2% by weight), glycerol (2.5% by weight) and sodium hydroxide to pH 8. The second emulsion was

prepared according to this invention. It had the following composition: 40% by volume perfluorodecalin and 60% by volume of a mixture of water (78.8% by weight), lecithin (1.2% by weight), glycerol (2.5% by weight) soy oil (17.5% by weight) and sodium hydroxide to pH 8. The two emulsions were prepared by mixing their components together in a Fisher brand touch mixer and then running them through a Microfluidizer for 30 min at 60 psi.

The first emulsion had a smaller average droplet size by optical microscopy than the second emulsion. It also had a higher concentration of water and thus less dispersed phase than the second emulsion. Accordingly, on those bases alone, we would have expected the first emulsion to be more stable than the second emulsion. However, the first "emulsion" was very unstable and exhibited phase separation at room temperature within 24 hours. The second emulsion (that prepared in accordance with this invention), while having a larger average droplet or particle size and more dispersed phase, was surprisingly very stable and showed substantially no phase separation and substantially no change in droplet or particle size distribution during 4 weeks storage at room temperature.

This comparison plainly demonstrates that the emulsions of this invention are different in kind from former compositions of highly fluorinated organic compounds. Not only are our emulsions far more stable, they are surprisingly more stable even with larger average particle or droplet size and more dispersed phase.

Example 2

We prepared an emulsion containing 40% by volume perfluorodecalin and 60% by volume of a first emulsion containing safflower oil (10% by weight), soybean oil (10% by weight), lecithin (1.2% by weight), glycerol (2.5% by weight), water (76.3% by weight) and sodium hydroxide to pH 8.3. We prepared the final emulsion by combining 20 ml perfluorodecalin and 30 ml of the first emulsion and mixing the combination in a Fisher touch-mixer for 20 min. We then ran the resulting emulsion through a Microfluidizer for 1 hour at 60 psi.

The resulting homogenized emulsion was still stable after 4 weeks at room temperature, as demonstrated by optical microscopy which indicated that there had been substantially no change in particle or droplet size distribution and substantially no phase separation.

Example 3

Using the substantially same process as described in Example 2, we prepared an emulsion containing 40% by volume perfluorodecalin and 60% by volume of a first emulsion containing safflower oil (10% by weight), soybean oil (10% by weight), lecithin (2.0% by weight), glycerol (2.5% by weight), water (75.5% by weight) and sodium hydroxide to pH 8.3. As before, the resulting emulsion was still stable after 4 weeks at room temperature.

Example 4

We prepared an emulsion containing 40% by volume perfluorodecalin and 60% by volume of a first emulsion containing safflower oil (10% by weight), soybean oil (10% by weight), lecithin (2.0% by weight),

glycerol (2.5% by weight), XMO-20 (see, e.g., United States patent 4,443,480) (0.1% by weight), water (75.4% by weight) and sodium hydroxide to pH 8.3. We prepared the final emulsion by combining 20 ml perfluorodecalin and 30 ml of the first emulsion and mixing the combination in a Fisher touch mixer until the lecithin and XMO-20 were completely dissolved. We then ran the emulsion through a Microfluidizer for 30 min at 60 psi. The resulting emulsion was still stable after 4 weeks at room temperature.

Example 5

We prepared an emulsion containing 40% by volume perfluorodecalin and 60% by volume of a first emulsion containing safflower oil (10% by weight), soybean oil (10% by weight), lecithin (1.2% by weight), glycerol (2.5% by weight), oleic acid (0.8% by weight), water (75.5% by weight) and sodium hydroxide to pH 8.3. We prepared the final emulsion by mixing 20 ml perfluorodecalin and 30 ml of the first emulsion in a Fisher touch mixer for 10 min and running the resulting emulsion through a Microfluidizer for 45 min. The resulting emulsion was still stable after 4 weeks at room temperature.

Example 6

We added lecithin to a final concentration of 2% (by weight) to the final emulsion of Example 5 and mixed it until the lecithin had completely dissolved. The emulsion was then run through a Microfluidizer for 30 min at 60 psi. The resulting emulsion was still stable after 4 weeks at room temperature.

Example 7

We prepared an emulsion containing 40% by volume perfluorodecalin and 60% by volume of a mixture containing water (78.8% by weight), lecithin (1.2% by weight), glycerol (2.5% by weight), soybean oil (17.5% by weight) and sodium hydroxide to pH 8.0.

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We prepared the emulsion by mixing 0.377 g lecithin and 20 ml perfluorodecalin in a Fisher brand touch mixer for 10 min. We then added 5.4915 g soybean oil and mixed again for 10 min and added 0.7945 g glycerol and mixed again for 10 min. Finally, we added 24.721 g water stepwise with mixing. We made this addition by first adding 12.36 g of water to the mixture to disperse the fluorocarbon-oil-lecithin mixture and emulsified the resulting dispersion in a Microfluidizer for 30 min at 60 psi. We then emptied the emulsion from the Microfluidizer and poured the remaining water into the Microfluidizer. After adding the previously prepared emulsion dropwise to the water, we ran the resulting mixture through the Microfluidizer for 30 min at 60 psi and adjusted the pH to 8.0 with sodium hydroxide. We then again ran the emulsion through a Microfluidizer for 30 min at 60 psi. The final emulsion was still stable after 4 weeks at room temperature.

Example 8

We prepared an emulsion containing 40% by volume perfluorodecalin and 60% by volume of a mixture containing water (78.8% by weight), lecithin (1.2% by weight), glycerol (2.5% by weight), hexadecane (17.5% by weight) and sodium hydroxide to pH 8.0. We used substantially the same method described in Example 7. The final emulsion was still stable after 4 weeks at room temperature.

Example 9

We prepared an emulsion similar to that of Example 8, except that hexadecane was replaced with mineral oil. Again, we used substantially the same method described in Example 7 to prepare the emulsion. The final emulsion was still stable after 4 weeks at room temperature.

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Example 10

We prepared an emulsion containing 55% by volume perfluorodecalin and 45% by volume of a mixture containing safflower oil (10% by weight), soybean oil (10% by weight), glycerol (2.5% by weight), lecithin (2% by weight) and water (75.5% by weight) and sodium hydroxide to pH 8. To prepare the emulsion we used 18 ml of the oil-containing mixture, 22 ml of perfluorodecalin and 1% (by weight on total) oleic acid. We used the method substantially as described in Example 7. We mixed the final emulsion for 20 min in a Fisher touch mixer and then in a Microfluidizer for 15 cycles at 65 psi. The emulsion was stable at room temperature.

Example 11

We prepared an emulsion containing 70% by volume perfluorodecalin and 30% by volume of a mixture containing safflower oil (10% by weight), soybean oil (10% by weight), lecithin (1.2% by weight), glycerol (2.5% by weight), water (76.3% by weight) and sodium hydroxide to pH 8.0. To prepare the final emulsion we used 21 ml perfluorodecalin, 9 ml of the oil-containing mixture, and 0.5% (by weight on total) oleic acid. As in Example 10, we used substantially the same method described in Example 7 to prepare the final emulsion. We then mixed the final emulsion for 20 min in a Fisher touch mixer and then in a Microfluidizer for 15 cycles at 65 psi. The emulsion was stable at room temperature.

Example 12

We prepared an emulsion containing 16.5 ml perfluorooctylbromide (55% by volume) and 13.5 ml of the same mixture of other components described in Example 11. We used the same mixing and fluidizing regime described in Examples 10 and 11. The final emulsion was stable at room temperature.

Example 13

An emulsion of perfluoro-cis-indane was prepared by mixing 10% by volume of the perfluoroindane in an intravenous fat emulsion, i.e., LIPOSYN II, manufactured by Abbott Laboratories. The LIPOSYN II is supplied in 10 and 20% concentrations. In this example, 10% concentration of LIPOSYN II is employed and contains 5% safflower oil, 5% soybean oil, up to 1.2% egg phosphatides added as an emulsifier and 2.5% glycerin in water for injection. Sodium hydroxide has been added to adjust the pH to approximately 8.0. LIPOSYN II 10% has an osmolarity of 320 mOsm/liter (approximate). The total caloric value of LIPOSYN II 10% including fat, phospholipid and glycerol is 1.1 kcal/ml. Of this total, approximately 0.6 kcal/ml is supplied by linoleic acid.

The perfluoroindane emulsion in this example was then injected into mice at a dose of 20cc/kilogram of body weight intravenously. Upon intravenous injection, there were no signs of toxicity and no evidence of gas or vapor embolism. It was also determined that the perfluoroindane left the animal body about five times faster than perfluorodecalin. More specifically, the average transpiration rate in microliters per day for perfluoroindane decreased from about 30 microliters/day upon infusion to a level of about 5 microliters/day at day 2, followed by rapid diminishment to less than 1 microliter/day after day 3.

By comparison, perfluoro-1,3,5-trimethyl-
cyclohexane was emulsified in a similar fashion at a
level of about 10% by volume within 10% LIPOSYN II and
injected into mice at a dose level of about 20cc/kilo-
gram intravenously. The average transpiration rate in
5 microliters/day was observed at a level of about 10
immediately after infusion to a level of about 5
microliters/day after day 1, and about 2½ micro-
liters/day after day 4. By comparison, therefore, the
10 transpiration rate of perfluoroindane is considerably
faster than the rate for perfluorotrimethylcyclohexane
which is considered an analog or sister compound.

In a similar fashion, perfluoroisopropyl-
cyclohexane was emulsified at a level of about 10% by
15 volume with 10% LIPOSYN II and mice were injected at a
dose of about 20cc/kilogram intravenously. As ex-
pected, the transpiration rate of the perfluoroiso-
propylcyclohexane was essentially the same as that for
perfluorotrimethylcyclohexane. However, by comparison
20 perfluoroindane has an unexpectedly faster rate of
transpiration or elimination from the body of the
mouse.

This example thus demonstrates that per-
fluoroindane may be injected into the animal body
25 without causing gas or vapor embolism. Moreover,
emulsions of perfluoroindane may be made and infused
intravenously to function in a gas transport manner
without toxic effects. Furthermore, upon comparison
with analogous compounds, quite unexpectedly, the
30 transpiration rate is significantly faster.

Example 14

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The procedures of Example 13 for perfluoro-cis-indane were repeated except that mice were injected with a dose of 40cc/kilogram intravenously of the 10% by volume emulsion with 10% LIPOSYN II.

5 Similar transpiration rates were observed with the larger dose of perfluoroindane except that larger amounts of perfluoroindane were being transpired post injection, namely, about 30 microliter/day at about day 1, about 17 microliter/day at day 2, about 10
10 microliters/day at day 3, about 4 microliters/day at day 4 and nearly 0 microliters/day at day 7. Otherwise, the experiments with mice injected at a level of 40cc/kilogram intravenously produced essentially the same results as those at the lower dose of 20cc/kilo-
15 gram according to Example 13.

While we have hereinbefore described a number of embodiments of our invention, it should be apparent that other embodiments also exist within our invention. Therefore, it should be understood
20 that the scope of this invention is to be defined by the claims rather than by the specific embodiments which have been presented hereinbefore by way of example.

CLAIMS:

1. An emulsion comprising a highly fluorinated organic compound; an oil that is not substantially surface active and not significantly water soluble; a
5 surfactant and water.
2. An emulsion as claimed in Claim 1, wherein the highly fluorinated organic compound is a perfluorocarbon, preferably, perfluorodecalin, perfluorodimethyladamantane, perfluorooctylbromide,
10 perfluoro-4-methyl-octahydroquinolidizine, perfluoro-N-methyl-decahydroquinoline, F-methyl-1-oxa-decalin, perfluoro-bicyclo (5.3.0) decane, perfluorooctahydroquinolidizine, perfluoro-5, 6-dihydro-5-decene, perfluoroindane, perfluoro-
15 trimethylcyclohexane, perfluoroisopropylcyclohexane or perfluoro-4-5-dihydro-4-octene.
3. An emulsion according to either claims 1 or 2, wherein said emulsion is stable after heating at about 115°C for about 15 minutes.
- 20 4. An emulsion according to any preceding claim wherein the oil is present in an amount between about 10 and 30%, preferably between 15 and 20%, by weight of the non-highly fluorinated organic compound volume of the emulsion.
- 25 5. The emulsion according to any preceding claim wherein the oil is a physiologically acceptable oil, preferably an oil selected from the group consisting of liquid fatty oils.
- 30 6. The emulsion according to any preceding claim wherein the surfactant is present in an amount between about 0.5 and 1% by weight, preferably about 1 and 2% by weight, of the non-highly fluorinated organic compound volume of the emulsion.

7. The emulsion according to any preceding claim wherein the surfactant is a physiologically acceptable surfactant, e.g. tecithin.

5 8. The emulsion according to any preceding claim wherein the highly fluorinated organic compound is present in an amount either between about 75% and about 10% by volume, preferably about 40% by volume.

9. An emulsion according to any preceding claim including at least one compound of the group
10 consisting of isotonic agents, osmotic pressure controlling agents, serum extending agents and antioxidants.

10. A red blood cell substitute comprising an amount of an emulsion according to any one of claims 1
15 to 9, said amount being therapeutically effective for oxygen carrying and transport in humans.

11. A contrast agent for biological imaging comprising an amount of an emulsion according to any one of claims 1 to 9, said amount being clinically
20 effective for imaging by modalities selected from the group consisting of nuclear magnetic resonance, x-ray and ultrasound.

12. A method for preparing an emulsion, comprising a highly fluorinated organic compound, an oil that is
25 not substantially surface active and not significantly water soluble, a surfactant and water, said method comprising the steps of preparing a first emulsion by mixing the highly fluorinated organic compound with the oil in the presence of all or a portion of the
30 surfactant and some of the water and preparing a final emulsion by emulsifying the first emulsion, the remaining water and any remaining surfactant.

13. A method according to claim 12, including the step of sterilizing the final emulsion by heating it

to about 1150C for about 15 minutes, said emulsion maintaining its stability under those conditions.

14. A gas transport agent liquid composition for infusion into an animal body without causing gas or vapor embolism comprising of perfluoroindane.

15. The composition of claim 14 comprising an aqueous emulsion containing emulsified particles of the perfluoroindane, an emulsifying agent in a non-toxic, non-haemolytic amount, and water, said particles contained in an amount sufficient to transport oxygen.

16. An artificial blood liquid composition for use without causing gas or vapor embolism consisting essentially of water, perfluoroindane and a surfactant.

17. A nuclear magnetic resonance contrast agent for use in an animal body without causing gas or vapor embolism consisting essentially of the emulsion as claimed in claims 1 to 9.

18. An emulsion as claimed in claims 1 to 9 for introduction into an animal body or isolated organ for supporting oxygen transport therein.

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European Patent
Office

EUROPEAN SEARCH REPORT

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Application number

EP 87 30 0454

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	EP-A-0 080 716 (THE GREEN CROSS CORP.) * Claims; pages 7-8 *	1-2,5 9-10, 18	A 61 K 9/10 A 61 K 31/02
D,X	US-A-4 252 827 (YOKOYAMA et al.) * Claims; columns 2-4 *	1-2,5 9-10, 18	
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Place of search THE HAGUE		Date of completion of the search 15-04-1987	Examiner VAN GEYT J.J.A.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			